Workshop on Inhibitors to Factor VIII

November 21, 2003

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2004-0033

Issues

Inhibitor formation to factor VIII is the chief adverse event associated with the use of antihemophilic products

How can we ensure that new factor VIII products, or products that have undergone significant manufacturing changes won't induce inhibitor formation in previously treated patients?

To what extent is immunogenicity a property of the product, rather than the patient?

Workshop Objectives

- Improve clinical trial design
- Review available data on the prevalence and incidence of inhibitor formation
- Examine the limitations and potentials of assays for factor VIII inhibitors
- Increase international harmonization
- Explore future directions and collaborative studies

Scientific and Regulatory Agenda

- Overview of factor VIII inhibitors
- Environmental and genetic factors that may influence inhibitor antibody formation
- What pre-clinical testing of factor VIII concentrates can tell us: A cautionary tale

<u>Inhibitor assay</u>

- Regulatory aspects of the factor VIII inhibitor assay
- Innovations in the factor VIII inhibitor assay

Scientific and Regulatory Agenda

- ISTH rationale of recommendations for use of previously treated patients (PTPs) in clinical trials

Inhibitor surveys

- Canadian experience with factor VIII inhibitors during conversion to recombinant products
- Occurrence of inhibitors among patients enrolled in the U.S. Hemophilia Universal Data Collection project

Scientific and Regulatory Agenda

Regulatory Considerations

- Requirements of the EMEA
- FDA recommendations for clinical trials
- Statistical considerations for design of FDA clinical trials
- Role of the data safety monitoring board in clinical trials

Scientific and Regulatory Agenda

Industry Perspectives

Baxter

Bayer

Biomeasure/Octagen

Wyeth

Future Directions

- Preliminary ideas on prospective international studies of product-related factor VIII inhibitor formation
- Panel Discussion

ENVIRONMENTAL AND GENETIC FACTORS THAT MAY INFLUENCE INHIBITOR ANTIBODY FORMATION

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Hemophilic Inhibitors

- Impact the outcome of replacement therapy
- Impact the assessment of efficacy and safety of new therapeutic replacement products
- Likely to impact the outcome of gene therapy
- Highly desirable to predict risk for inhibitor development and to identify factors that predispose to inhibitor development

Evidence for Genetic Factors in Inhibitor Development

- Inhibitors develop early, within a median of 9-11 exposure days to replacement therapy suggesting a predisposition to inhibitors
- Increased inhibitor risk in African Americans
- Animals Studies: Introduction of out-bred female into hemophilic dog colony resulted in progeny with inhibitors; Differential development of inhibitors in hemophilic mice strains

Hemophilia Sib-Pairs:

Preliminary data from 392 brother pairs from 54 centers in the US and Canada

	Total N	N Inhibitor	% Inhibitor
Hemophilia A, Severe	255	96	38
Hemophilia A, Moderate	57	7	12
Hemophilia B, Severe	47	1	2
Hemophilia B, Moderate	33	0	0

Observed vs Expected Inhibitors in 255 Severe Hemophilia A Brother Pairs

# Sons Hemophilia	# Inhibitor Sons	# Observed Families	# Expected Families Inhibitor =15%	# Expected Families Inhibitor = 20%
2	2	[illegible]	[illegible]	[illegible]
	1	55	60	76
	0	153	171	151
3	2 or 3	3	1	1
	1	3	6	7
	0	13	12	10
?[2]			113.7	53.1

Gill, 1999

Malmö International Brother Study

- 460 families (388 hemophilia A)
- Overall inhibitor incidence - 31.7%; Caucasians - 27.4%; Blacks - 55.6%
- Concordant Inhibitors - 78.3% (Expected - 58% for inhibitor incidence of 20% and 68% for 30% incidence)
- Risk if family history - 48%

Astermark, 2001

Inhibitor Formation by Factor VIII Mutation Type

Genotype	Severe, %	Mild/Moderate, %
Deletion>200 bp	32	-
Point	23	3
Inversion	35-40	-
Deletion<200 bp	6	-
Insertion	8	-

Tuddenham, 1998

Effect of Mutation Type on Inhibitor Development

Mutation	Total N	N Inhibitor (%)
Intron 22 Inversion +	642	130 (20)
Intron 22 Inversion -	821	131 (16)

Antonarakis, 1995

Incidence of Inhibitors in Extended Families

Hypothesis: Since each hemophilic member of a single family has the same factor VIII mutation, if additional important genetic factors play a role, the risk of inhibitor development should be greater in the hemophilic siblings of an inhibitor patient than in his extended hemophilic relatives (grandfathers, cousins, nephews, and grandsons)

Risk of Inhibitor Development in Brothers Vs Extended Family Members: Hemophilia Research Society Inhibitor Registry

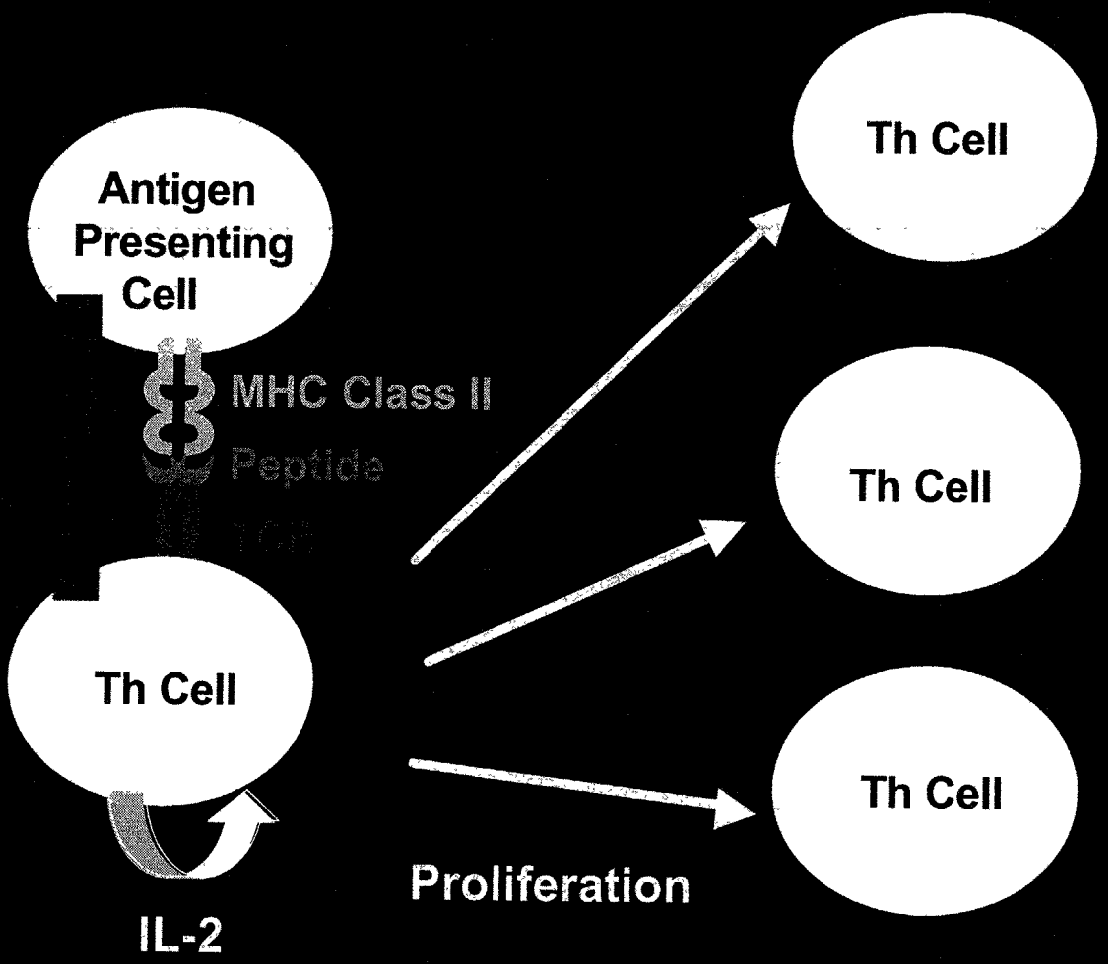
- 113 Inhibitor patients with severe hemophilia A
- 47 (41%) One or more family members with hemophilia
- 52% risk of inhibitor if sibling with inhibitor
- 14/131 (11%) extended family members with inhibitor
- 4/47 (9%) extended family members of sibling pairs with inhibitors

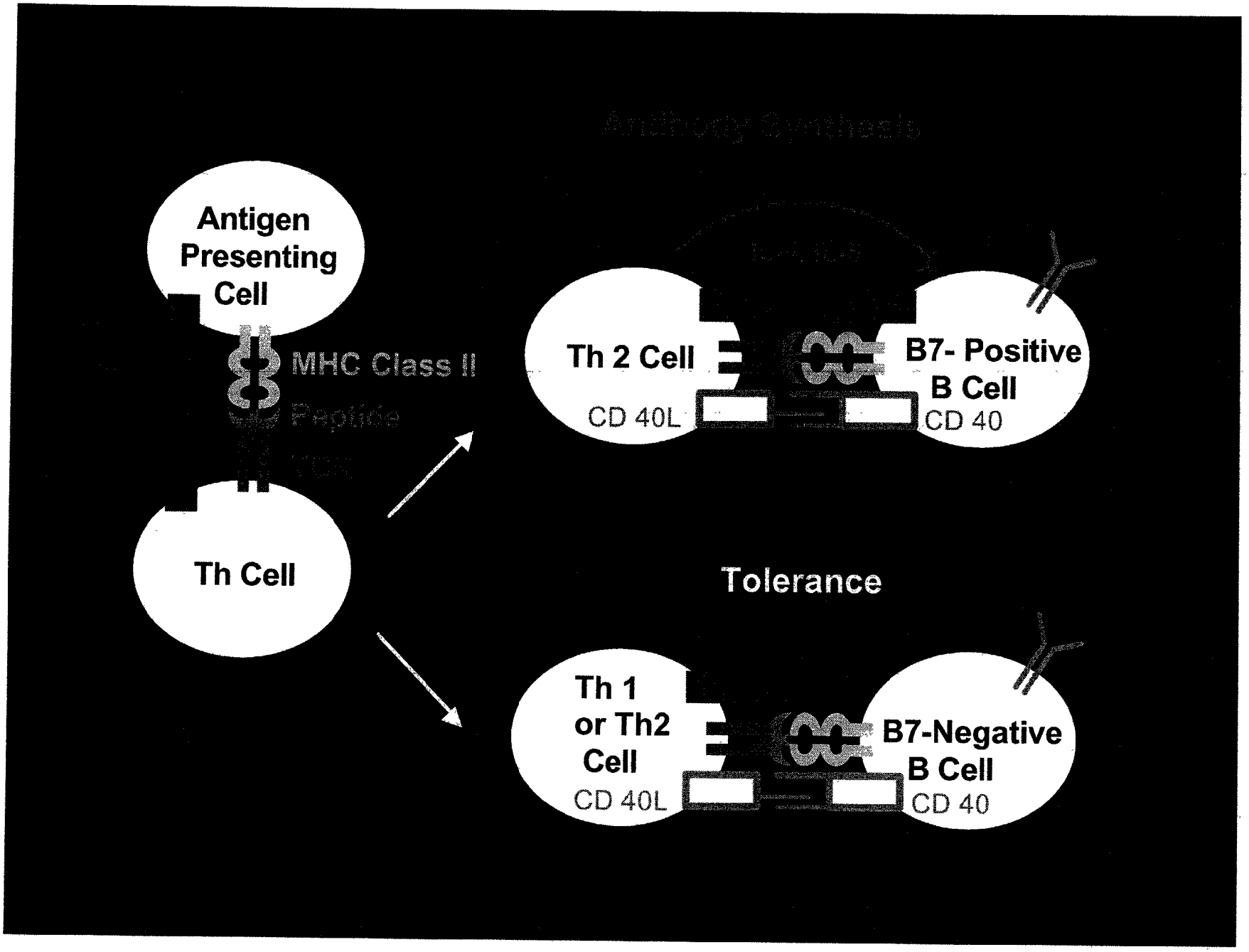
Gill, 1999

Evidence for the Role of T-Cells in Inhibitor Formation

- Concomitant disappearance of inhibitor with loss of CD4+ helper T-cells in HIV infection
- IgG4 predominant isotype of inhibitors: evidence for "Th-2-like" nature of the response, i.e.requires T-cell help for B-cell differentiation and immunoglobulin isotype switching
- Tolerance to factor VIII can be induced in inhibitor patients
- Tolerance induction by blocking accessory molecule interaction in mouse models

Th Cells Secrete IL-2 Upon Recognition of Peptide/MHC




Antigen Presenting Cell
MHC Class II
Peptide
TCR
Th Cell
Th 2 Cell
CD 40L
B7- Positive B Cell
CD 40
Tolerance
Th 1 or Th2 Cell
CD 40L
B7-Negative B Cell
CD 40

Inhibitors and HLA

- No significant difference in DR type in hemophilic patients with and without inhibitors, N = 65 (12 inhibitor +) (Mayr, 1984)
- No difference in DR type in inhibitor vs non-inhibitor patients (Lippert, 1990)
- Absence of HLA-Cw5 in inhibitors but no difference in DR types (Aly, 1990)
- Weak increased association of DQA1*0102 in inhibitor patients with (OR 2.7, 1.2-5.9) or without (OR 3.1 (1.0-10.1) intron 22 inversion mutations (Hay, 1997)
- No strong correlation of any HLA-allele to inhibitor or non-inhibitor status with intron 22 inversion (Oldenburg, 1997)

Candidate Genes

- MHC
- Immunoglobulin genes
- TCR genes
- Cytokine and cytokine receptor genes that define Th cell subsets
- Accessory molecules

Factors that may Predispose to Inhibitor Formation:
Non-Genetic

- type and purity of factor concentrates
- age at initial therapeutic exposure
- dose and frequency of initial therapeutic exposures
- "in utero" exposure?
- exposure to homologous proteins in breast milk
- concomitant illness/medications (e.g. HIV infection)

Type and Purity of Initial Factor VIII Concentrate Exposures
(Analysis of Thirteen Published PUP Studies)

	Weighted Mean % Cumulative Risk All Inhibitors	Weighted Mean % Cumulative Risk High Responders
Multiple Low/Intermed Purity pd Concentrates	25.9 (20.3 – 33.0)	21.9 (19.2 – 26.4)
Single pd Concentrate	6.8 (0 – 12.4)	1.4 (0 – 2.5)
Recombinant Concentrate	37.5 (36 – 38.7)	15.1 (11.3 – 18)

Wight, 2003

Cumulative Risk of Inhibitor Development in Severe Hemophilia A PUPs Treated with Recombinant FVIII Concentrates

Study	Cumulative Risk	Median Age	Median Exposure Days	Product
Lusher	30	1.6	9	Kogenate
Bray	31	1.6	10	Recombinate
Lusher	30	1.3	12	ReFacto

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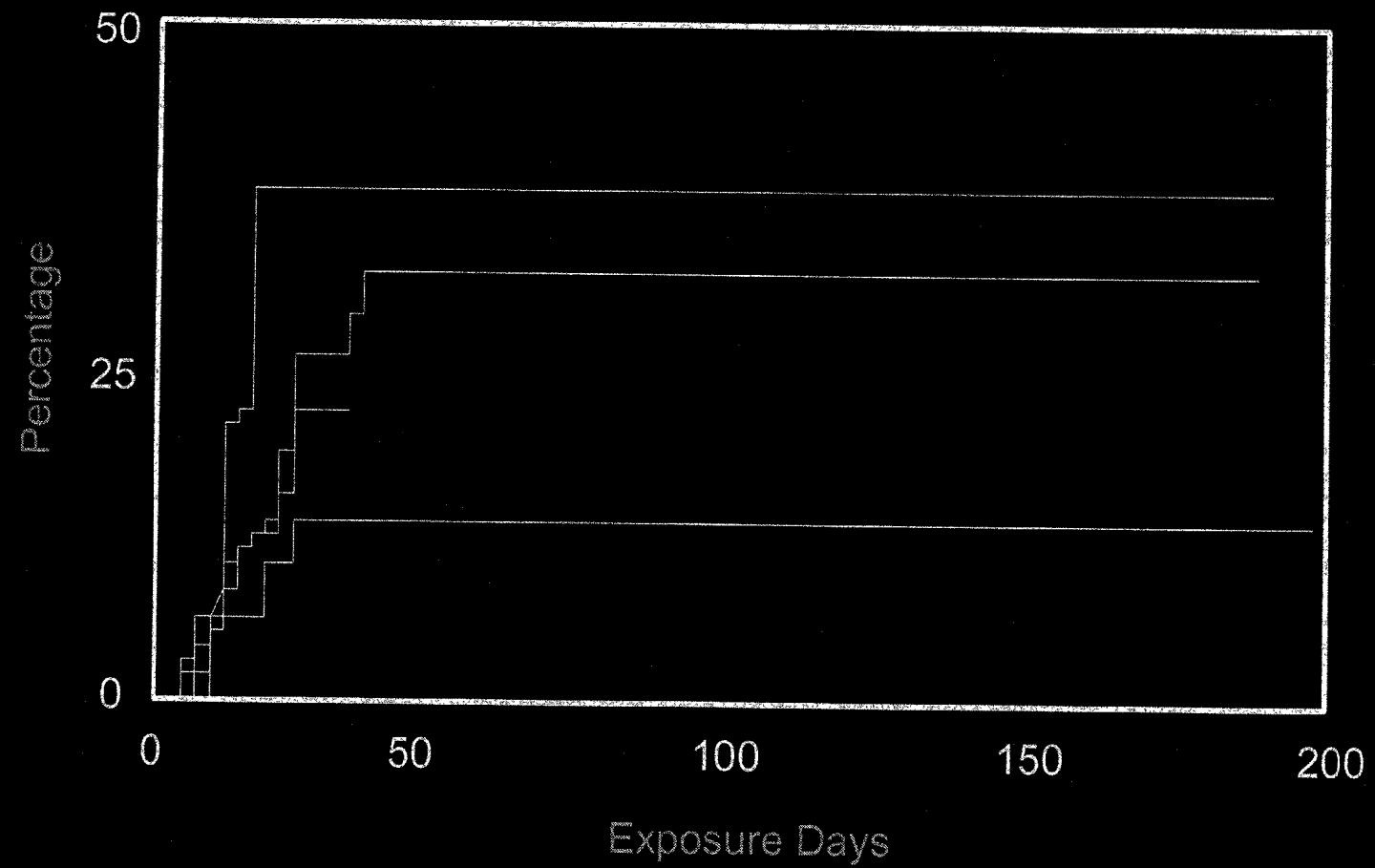
Cumulative Risk of Inhibitor



What information from the study of inhibitor formation in PUPs can be applied to the study of inhibitor formation in PTPs?

- Long term natural history of inhibitor incidence (new and disappearing) in patients treated with single products vs multiple products
- Careful follow-up of patients during a switch to a new product
- Evaluation of the effect of illnesses and medications on inhibitor development during product changes

Important Variables to Evaluate in PUP and PTP Studies

- Hemophilia mutational analysis
- Ethnic background
- Family history of inhibitors
- Previous history of inhibitors
- Immunologic disorders/medications
- Inflammatory disorders at the time of exposure